Differentiators When Choosing Novel TreatmentOptions for EDS

CMEO Podcast Transcript

Richard Bogan:

Hello, I'm Dr. Richard Bogan, and on behalf of CME Outfitters, I would like to welcome and thank you for joining us for episode three of the four-part CME O-cast series, fine tuning diagnosis and management of EDS and patients with narcolepsy and obstructive sleep apnea. Today's episode is titled, Differentiators when Choosing Treatment Options for EDS. This activity is brought to you by CME Outfitters, an award-winning accredited provider of continuing education for clinicians worldwide.

Again, I am Dr. Richard Bogan, president of Bogan Sleep Consultants, medical officer of SleepMed Incorporated, and director of SleepMed of South Carolina. I am also the associate clinical professor at the University of South Carolina School of Medicine in Columbia, South Carolina, and associate clinical professor at the Medical University of South Carolina in Charleston, South Carolina. I'm very pleased to be joined today by a national and international expert, Yves Dauvilliers. He's professor of neurology and physiology at the University of Montpellier and director of the Sleep-wake Disorders Center, Department of Neurology, Gui de Chauliac, France. Welcome Yves.

Yves Dauvillier...:

Thanks Rick.

Richard Bogan:

So to frame today's episode, let's start by reviewing our learning objective, which is to apply efficacy and safety data to treatment decisions for EDS in patients with obstructive sleep apnea or narcolepsy to improve quality of life and functioning. Of course, narcolepsy patients are profoundly sleepy and give us some insight into sleep-wake processes because of the pathology and obstructive sleep apnea patients are profoundly sleepy. The majority of them aren't, it's one of the most prevalent disorders that we see in the sleep clinic, right along with insomnia, but it's a prevalent disorder and many of the patients still have sleepiness despite our best efforts to treat those patients. So I'd like to begin our discussion today with the treatment goals in narcolepsy and obstructive sleep apnea. Yves, can you share this with our audience?

Yves Dauvillier...:

Yes, for sure. Thanks, Rich. So the treatment goals to treat EDS, especially narcolepsy, I know that need to be the first key target because these are really building symptom that may change the quality of life of this two population. But we need also to think a little bit more louder and not just to treat daytime sleepiness, but to control other symptoms associated with narcolepsy, or within OSAS, and for narcolepsy, especially we need to control also cataplexis, leprolisis, hallucination in both condition OSAS and narcolepsy, we need to improve this term, nighttime sleep, as it being often very disturbed in this two condition. Fatigue and brain fog are also really problematic in most of patients with narcolepsy or OSAS. And they are all affected with psychosocial dysfunction and bad quality of life, and this is a target we need to focus on. And the final goal is to standardize the follow up and to optimize the benefits switch ratio with the different drugs we will provide.

Richard Bogan:

Yeah, thank you. I like your discussion about personalizing care of... Each patient has their own set of symptoms and of course, sleepy individuals, not only are sleepy, but they're tired and they have problems with executive function thinking, memory focus, mood, productivity, fatigue related accidents. So each of those bother patients in a different way and of course, we approach the patients behaviorally. But obviously we have multiple new medications available to us and we can achieve some of our goals through pharmacotherapy. Can you talk to us about FDA approved treatments for excessive sleepiness, both obstructive apnea and narcolepsy patients?

Yves Dauvillier...:

Yeah, so we are very lucky right now to have several drugs to treat daytime sleepiness in OSAS and narcolepsy. We do have modafinil or armodafinil sodium oxybate. There's a new one, the low salt has got Xywav, so sodium oxybate low salt, solriamfetol and pitolisant is quite some different approval and for sure different mechanism of action. Modafinil, and armodafinil are just for adults in narcolepsy and OSAS. And sodium oxybate, the recent one, the low salt, is for patient with narcolepsy and also in kids above seven years old. Solriamfetol and pitolisant, it works in managing EDS in adults. And for solriamfetol it also approve for EDS in the condition of OSAS in contrast to pitolisant.

Richard Bogan:

Excellent, can you begin to explore some of the data that actually the FDA used to approve these drugs? I mean, demonstrate efficacy. Let's begin with modafinil, armodafinil.

Yves Dauvillier...:

Yeah, so modafinil is a French drug, as you know, is known for 25 years. So it's a a long story. And to be short, it works compared to placebo in decreasing the Epworth Sleepiness Scale being of a very often primary endpoint measure, a self-report questionnaire that assessed the sleepiness of the patient complain. And it increased the NWT, being a test to, of Humira four time during the day, the ability to fight against sleepiness, which is an objective measurement of sleepiness. And as you can see here probably on this slide, there is a increase of 2.5 minutes, three minutes, depending on the dose with modafinil compared to the placebo. So modafinil and armodafinil works in the same way, the only difference is that armodafinil is a long player action with just one intake in the morning.

Richard Bogan:

Yeah, those are those two drugs really changed the landscape of our treatment of patients with excessive daytime sleepiness. And we appreciate the French scientists for introducing us to this drug, these drugs. And what about solriamfetol? ... Excessive sleeping and the narcolepsy and the obstructive sleep apnea.

Yves Dauvillier...:

Yeah, solriamfetol is a newer player in the game and is really helpful with several studies has been done on randomized controlled trial and to prove that it works compared to the placebo dose dependently. And also there is a one open label study for one year that show that there is a maintenance of efficacy based on the complaint is same, a primary end point, the Epworth Sleepiness Scale, and we do see a reduction of this scale for five to seven points. And the big news is that it, that persist after one year.

Yves Dauvillier...:

They also perform a two weeks randomized [inaudible 00:07:08] at the end of the trial to prove that there was a rebound of the complaint of sleepiness, if you are randomized to the placebo and if you keep the drugs with you, there is no change too. I think it's promising.

Richard Bogan:

Yeah, it's an interesting drug. And I think the data supports the idea that we're not really seeing tolerance within the limits, we're not seeing tolerance and rebounding withdrawal in these individuals. And as you pointed out in your previous discussion about neurobiology, its effect on norepinephrine and dopamine, re-uptake seems to be the mechanism of action for this monoaminergic process. But in continuing with the solriamfetol, we know patients with cataplexy tend to be sleepier, at least that's my impression that they're sleepier than the ones without cataplexy, does the work? Does the drug work both in type one and type two?

Yves Dauvillier...:

Yeah, it's good point. We just covered a topic that it works in narcolepsy and in OSAS associated with EDS, but we also did a study confirming that it works on narcolepsy with, and without cataplexy. Patient was cataplexy have mostly more severe sleepiness at baseline based on this NWT and the Epworth Sleepiness Scale, but the amplitude of change, with solriamfetol, is nice in the two condition with again, different, neurobiology and in the background in term of orexin deficiency. So yes, it works in, in narcolepsy with, and without cataplexy, was in the same direction.

Richard Bogan:

Yeah, good point. And of course, it does. We don't have any evidence that improves cataplexy, but certainly the sleepiness in these very sleepy individuals. But what has the data shown in terms of the impact of solriamfetol on quality of life and functional outcomes, workplace performance, driving these, individuals who are sleepy have problems with this?

Yves Dauvillier...:

Yeah, though, there's the nice study is based on the randomized control trials on 12 weeks, follow-up that showed that there is an improvement in driving performances, the functional outcome, based on another end point scale nameless [inaudible 00:09:20] is of interest to look, especially at the ability to drive, and it is improved with the solriamfetol compared to placebo. And we were also interested in looking at the productivity as absenteeism, presenteeism, and it seems to be well-managed with solriamfetol compared to the placebo. So I, we may say that based on different measurement, it improves sleepiness, but it improve also what is related to sleepiness in terms of functioning. Functioning to work, functioning, to drive and ability also in term of quality of life, mostly related to family issue. So yes, it's good in term of global activity.

Richard Bogan:

Yeah, I think, excuse me, the workplace performance data is very interesting. I think we now have pitolisant, another French drug. So another FDA approved drug to treat excessive sleepiness and narcolepsy. This is a new drug. What have we learned about its efficacy?

Yves Dauvillier...:

Yes, it's a new drug in US, less new in Europe and there's several studies, at least in two major condition. One is narcolepsy, the other is a daytime sleepiness in OSAS, and most of the results show that it works on the same endpoint again, the Epworth Sleepiness Scale, on the 12 weeks follow-up. So that's three months as done for most of randomized controlled trial. And we do have also one study with one year follow-up showing that it works also with the persistence of efficacy with mounts. There is no these two weeks randomized period as compared to the solriamfetol but the open label studies show that the persistent of efficacy is still there after one year.

Richard Bogan:

Yeah, I know you have a lot of experience with this drug and we also know patients with obstructive sleep apnea, certain subgroup of those individuals are still sleepy and you've done some research on that. Could you share those results?

Yves Dauvillier...:

So, yeah, so pitolisant works also on daytime sleepiness in patient with OSAS in two different way. So as we discussed last time, pitolisant works in increasing histamine in the brain in blocking the receptor of the transporter of histamine, the presynaptic level. So when you give pitolisant to the patient, you increase histamine in the brain.

Mostly you can increase also some other neurotransmitters, but at a lesser extent, and the results show that the patient may be improved in term of sleepiness in two ways. One is, patient that are still sleepy, despite the fact that CPAP machine is well done in term of good adherence, good compliance and no persistent of AHI. And there is also a recent study that proved that it works also in patient who cannot cope with the CPAP machine, but they are still sleepy. They are still sleepy because of OSAS, you exclude all the many conditions that makes blink sleepiness in OSAS again, the oppression of SSE sleep deprived, but the patient cannot cope with any management in term of autism and a CPAP machine. But they are sleepy and you need to improve them, and it works. So I... And there is no key side effect, we will discuss that later, but there is no key side effect in this population specifically. So I think it's nice also to think about these drugs for idiocy knows us.

Richard Bogan:

Yeah, I think we'll be waiting for more data on pitolisant in this indication as, and I should point out, of course, it's not approved in the US for the treatment of excessive sleepiness and OSA, but this is evolving science, and certainly I wanted our group to have a chance to hear that. Of course, sodium oxybate is another agent that's been widely used in excessive sleepiness and narcolepsy and particularly cataplexy, but also disrupted nocturnal sleep and REM dissociative, other REM dissociative symptoms and the EDS. What have we learned about its efficacy, both in children and in adults?

Yves Dauvillier...:

So yes, this is quite known for around 15 years old, right now in adult, that exactly what you say, it works on cataplexy, it works on disturb nighttime sleep, and it works on sleepiness. But recent studies has been done in kids in again, in randomized withdrawal period, just to minimize the exposure to placebo in the patient and for two weeks, the patient with the placebo, but for the remaining period, they are treated with sodium oxybate and also on the long-term level, because the studies has been confirmed with an open one year follow-up and we confirm exactly the same results as in adults.

Yves Dauvillier...:

So a decrease of sleepiness, decrease of cataplexy and improve of nighttime sleep. But today we discuss on sleepiness and yes, it works on daytime sleepiness based on this Epworth Sleepiness Scale, adapt for kids because it's not exactly the same level.

Richard Bogan:

This was a very humane study because maintenance of effect, you've got to treat the patients and then had that two week withdrawal period and so, very, very interesting, and sometimes it's hard to interpret that data, that withdrawal data. What about JCP 258? It's now a low salt oxidate and was recently approved in July, in the US, for excessive sleepiness and narcolepsy, as well as cataplexy. What did we learn from the clinical trials?

Yves Dauvillier...:

Yes, it's very new and exciting drugs, not in terms of mechanism of action, because it's all the same as XYREM. But it's low salt, so it's of interest in term of risk and to limit the exposure of 1.5 grams of sodium per day, for those treated with nine grams of sodium oxybate. So the study was complex, we have no time to discuss on it, but there are four different groups you can be treated with sodium oxybate when you entering the study, treated with anti-cataplexy drugs, namely antidepressant, or drug free, or the combination of antidepressants and XYREM, and also stimulants that may be also in the study if you add the same dose during the wool study, so there's different groups.

And for this discussion of today, it works on sleepiness that confirmed exactly what we did already measure on using sodium oxybate. So it works on cataplexy, it's not the topic of today, and it works on daytime sleepiness in the four different group I just refer to you. So it's a complex study because of the heterogeneity of the population. And again, it was a withdrawal for two weeks, randomized withdrawal study to confirm that the Epworth Sleepiness Scale will change. If you are randomized to the placebo or to the GCP 258, name Xywav, for those who are not yet familiar with.

Richard Bogan:

Yeah, I think your point is well taken. It's 92% less salt. And again, this was a humane study from the perspective patients were allowed to continue on their stimulants. In maintenance of effect, you could adjust the dose and then we have this two week randomized withdrawal period, show the improvement in sleepiness and quality of life, quite frankly, in the individual. So I would encourage those to dig into the data and thank you for that summary. So, and again, thank you for this great overview of these agents for excessive sleepiness and narcolepsy and obstructive apnea, but we also need to talk about their side effects. Can you tell us about potential side effects in these individuals... In these drugs?

Yves Dauvillier...:

Yes. For sure, when you have some benefit with drug, you have safety concern of interest to be known for all physician, because you cannot have benefit if you have no risk, and so you need to balance that. And for most of these drugs we discuss on there, is some side effect with anxiety, with decreased appetite, with stress, with headache, with insomnia. And so this is the major side effect.

Yves Dauvillier...:

So depending on the drugs again, and the dose and the population target, this is OSAS or narcolepsy, we cannot review everyone, but I may say that generally speaking, anxiety, decreased appetite, headache and nervousness, insomnia, maybe we need to think about it and to adapt the dose when it is mandatory to do so.

Richard Bogan:

Yeah, good point. I mean, we worry about... These obviously have CNS effects. And when we look at research, we look at group data and they're always outliers. So it's really important for us to follow our patients and monitor for, CNS, adverse events and plus the potential effect on the sympathomimetic system, so heart rate and blood pressure, those are always tremor and anxiety, those are always things that we keep in mind. So, given the side effect profiles of these agents, are there any special considerations that healthcare providers need to keep in mind?

Yves Dauvillier...:

So, yes, I think there is, in addition to the classical side effect, we need to think about specific side effect and modafinil is often the first treatment, first-line therapy, we propose to treat EDS in this population, and we really need to be cautious about young female because of hormonal contraceptive agent, and there is a interaction between modafinil, armodafinil and this contraceptive agent that, that is a specific concern for modafinil.

For solriamfetol, I think that we need also to think about the blood pressure monitoring, and sometime you need to go a little bit further with ambulatory blood pressure monitoring, to be sure that there is no high blood pressure because of the drug is almost the same with modafinil, but solriamfetol is a new one in the field, so we need to target that more closely.

For pitolisant, I think that there is less side effect in term of the risk pour of blood pressure and hormonal contraceptive issue seems to be less problematic than modafinil, but is not 100% clear so far.

And for sodium oxybate, I think we need to have a... This risk for height, high sodium formulation that had too much salt on daily basis. But of interest, we need to think about the decrease in body mass index. And it could be a big concern in kids, half of them and in adults once sort of them, in patient with narcolepsy. So to decrease body mass index could be finally a good side effect. And with the 258, the problem of sodium will be for sure, normal there, because there is 92% decrease.

Richard Bogan:

Excellent. So, treatment selection can really be a challenge for clinicians managing excessive sleepiness. So you've discussed efficacy data and safety data, the pharmacotherapies. Based on your clinical experience, are there any special consideration? I know this is soft, but are there special considerations that you have in terms of personalizing therapy?

Yves Dauvillier...:

Yes, thanks for this very important question about the personalized medication. There is a lot of drugs right now, at least six drugs on the market, and for which patient do we need to use which drug? So it's almost impossible to really answer this important question because there is no head to head comparison studies except modafinil and pitolisant in one, studied in narcolepsy.

Yves Dauvillier...:

So it's mostly based on experience in the field and what we have in mind, especially my lab, that we make a consensus at the French level to try to propose the first step second step on second-line therapy for the treating EDS in narcolepsy. And in favor of modafinil, we add in mind that patient need to be with severe EDS and mild cataplexy, because it's not really effective on cataplexy as you know, and low cardiovascular risk profile.

For pitolisant, there is no risk in term of cardiovascular problems, so it could be proposed in this specific population, but this is the point and for cataplexy is in between and sometime and clear, so patients with probably not a good target to go there.

With solriamfetol, is quite new, so it's hard to really make some recommendation, but it seems to be very active on daytime sleepiness, but not on cataplexy and with some concern about blood pressure.

For sodium oxybate, we know quite that well. So, for severe cataplexy is lovely for... But it's sometimes not enough for severe time sleepiness, it may be just for moderate daytime sleepiness and be cautious also that the blood pressure. And for obese patient could be nice because of side effect in decreasing BMI.

For methylphenidate, could be nice because of this problem of contraception for young females. And this seems to be a very effective drugs to treat severe daytime sleepiness.

And for the 258, it's almost the same indication of sodium oxybate, and especially for those with comorbid cardiovascular disease because of this daily salt decrease.

Richard Bogan:

Yeah, certainly. And to reemphasize, pitolisant in the US is not scheduled, so they have very low abuse potential. Solriamfetol is a schedule four drug... And does not appear to have any interaction with oral contraceptives either, so that's a potential advantage in that situation. With a methylphenidate, we always worry about tolerance and rebound in withdrawal in the patient, so. Then we have special populations. We have children, we have elderly patients, pregnancy. Do you have any specific considerations or that are important in terms of treatment selection and some of these subpopulation?

Yves Dauvillier...:

Yes, it is exactly what we need to go in the next five or 10 years, I don't know, but for which drug for which population, so I try to sum up very briefly and probably too briefly about the comorbid condition in term of the background, severity of EDS or cataplexy, nighttime sleep, comorbidity in term of BMI, psychiatric problem, and cardiovascular problem.

But we may also discuss about kids, about elderly, about pregnancy, about anesthesiology, which kind of drugs do you need to propose in this specific population. And also, especially for a refractory patient, we do see more and more in tertiary university hospital, the more severe patient, and they cannot be managed with one drugs, and you need to combine drugs and you need to probably to combine drugs with different mechanism of action. Because if you go with just one mechanism of action, it cannot be enough. And the long-term management is also a big concern because you cannot speculate the efficacy after five years when you have no data. And the randomized control trial show up often good efficacy even after one year, but what about 10 years, 20 years? And the long-term management need to be really answer and it is not done today.

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Richard Bogan:

Yeah, I think I'm impressed with the European follow-up and patients to give us some insights in that quite frankly, long-term utilization, particularly some of the data that's been presented on long-term use of pitolisant and polypharmacy. So, I think that's been very helpful too, for us in terms of managing these patients long-term. So, Yves, thank you for providing us with a great overview of the latest clinical evidence on the safety and efficacy of current and novel therapies for EDS and narcolepsy or obstructive sleep apnea. Now, let's close with our smart goals that is, specific, measurable, attainable, relevant, and timely goals. Yves, what do we hope the healthcare practitioners listening today will take away from this podcast?

Yves Dauvillier...:

So, yes, thanks, Rick. I will sum up with four goals. The first is to develop personalized, effective strategy to reduce daytime sleepiness in patient with OSAS and narcolepsy. We need to consider the comorbidities, we discuss that depression, obesity, cardiovascular disorder, to make a good selection of which drugs as a first choice, second choice. We need think, especially with those with cardiovascular problem, hypertension even more cardiovascular disorder to use a low sodium oxybate, and that include safer drugs on the daily practice.

And the main, last important point is to standardize and personalize the follow-up to really be sure of the efficacy with nice tools we discuss on Epworth Sleepiness Scale, but I think it's nice to discuss also on the narcolepsy severity scale because it's covered not just the daytime sleepiness problem, but also cataplexy, hallucination, and disturb nighttime sleep. CT is for the benefit aspect, but for the safety aspect, you need to see the patient on the... At least twice a year, and to look for depression, the BMI, the blood pressure, and to be sure that the benefits risk ratio is always good enough to continue the medication or to think about changing because we have several player right now that may help to treat a patient on the long-term level.

Richard Bogan:

Yeah, excellent Yves. I can't thank you enough for sharing your scientific knowledge and more importantly, your learned experience with us. To receive CME or CE credit for this activity, click on the link identified here, to complete the post-test and evaluation online. And also please visit the sleep disorders hub @cmeoutfitters.com, sleep disorders hub, for additional educational activities, resources, and tools to improve the care of patients with excessive daytime sleepiness. Thank you for joining us today for episode three of our four-part CME O-cast series.

To view additional episodes on an overview of EDS and the burden it imposes, matching treatment choice to the path of physiology of sleep and diagnosing and treating pediatric narcolepsy with cataplexy, please visit CME outfitters.com.

Thank you again for participating and thank you for providing the best care for your patients and a special thanks to Yves for his expertise and sharing his knowledge. Thank you very much.

Yves Dauvillier...:

Thanks Rick, again.